# THE SYNTHETIC POTENTIALITIES OF NITRILES IN HETEROCYCLIC SYNTHESIS

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Abstract- The synthetic potentialities of nitriles as synthons for a variety of heterocycles are surveyed.

## INTRODUCTION

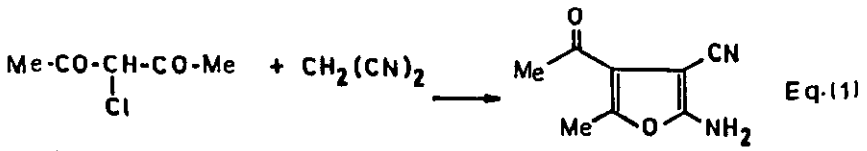
Organic cyano compounds are versatile reagents which have been extensively utilised in heterocyclic synthesis. Enormous number of reports on the utility of these compounds in synthesis of heterocycles has been reported. However, to our knowledge, this subject has been efficiently surveyed only up to 1970 by Mayers and Sircar[1]. After 1970, literature survey reveals a rapid development in the chemistry of organic cyano compounds. Recently, the utilities of $\alpha,\beta$-unsaturated nitriles, 3-oxoalkanonitriles and of cyanoacetic acid derivatives in heterocyclic synthesis have been reviewed[2-4]. Also, Freeman has surveyed, among other topics, the utilities of malononitrile and malononitrile derivatives in heterocyclic synthesis[5,6]. It is our intention in this article, therefore, to fill the gaps and report on the utilities of organic cyano compounds which have not been surveyed before. We hope that such review article would demonstrate the importance of nitriles as versatile reagents and intermediates in heterocycle synthesis and that it would be of value for both researchers and instructors of heterocyclic chemistry. It should be pointed out here, however, that no trial to make an encyclopendic scan of the whole subject was made.

### i. Synthesis of Five-Membered Heterocycles:

#### 1. Synthesis of Five-Membered Rings with One Hetero-Atom:

##### a. Synthesis of Furans:

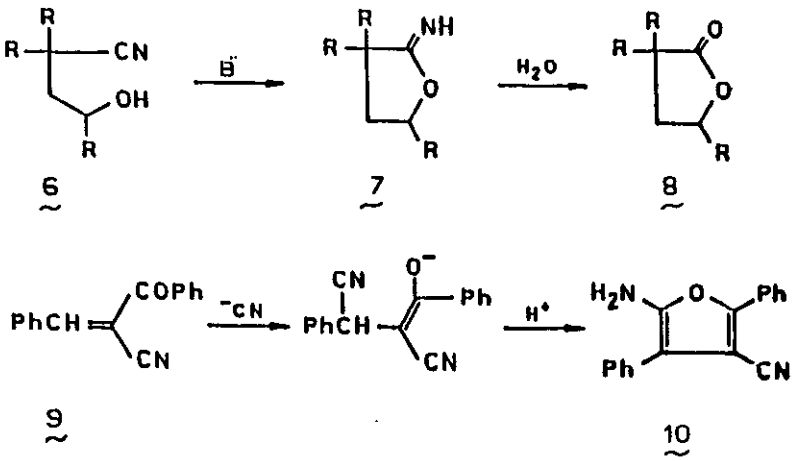
The reaction of $\alpha$-haloketones with active methylene nitriles has extensively utilized for the synthesis of furans. For example, the reaction of $\alpha$-chloroacetylacetone (1) with malononitrile affords the furan derivative (2) in more than 60 % yield[7,8] (cf. Eq. 1). Also, the condensation of $\alpha$-hydroxyketones (3) with cyanoacetic esters or malononitrile (4; X = COOEt; CN) affords the furan derivatives (5)(cf.Eq.2)[9-11].



Eq.(1)

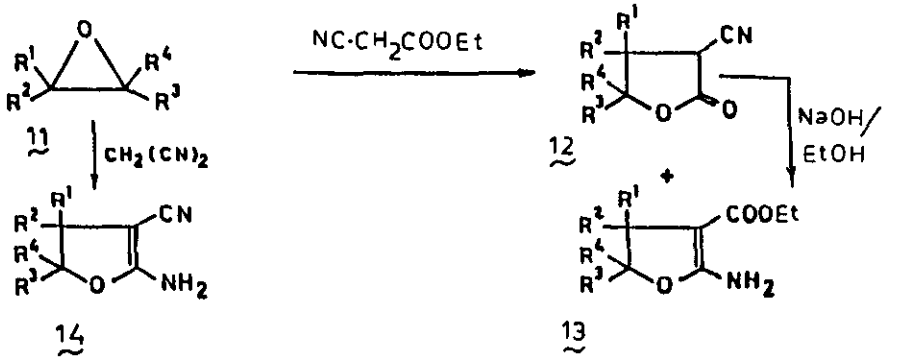
Eq.(2)

$\gamma$-Hydroxynitriles (6) usually cyclized into the corresponding furanones (8) on treatment in basic media. The reaction is believed to proceed via intermediacy of (7) (cf. Scheme 1)[12]. Very similar to this is the reported formation of the furan derivative (10) on reacting (9) with cyanide ion (cf. Scheme 1)[13]. It is of interest to note that the hydroxynitriles (6) which is capable of forming five membered rings, do not show any nitrile stretching band in the IR spectrum. This supports the believe that these compounds exhibit ring chain tautomerism and the equilibrium shifts towards the cyclic structure[14].



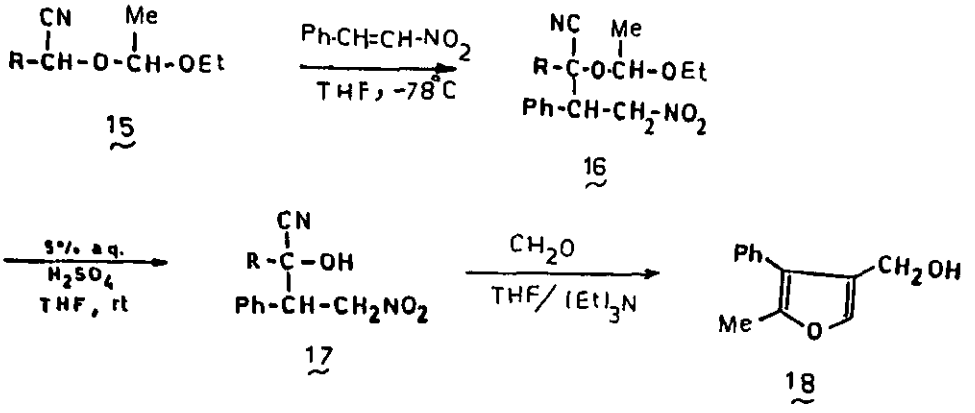
Scheme(1)

Ethyl cyanoacetate reacts with oxirans (11) to yield a mixture of cyanolactone (12) and the enamino ester (13)[15,16]. Compound (12) could be converted almost quantitatively into (13) on treatment with ethanolic sodium hydroxide[17-19]. The reaction of oxiranes with other activated nitriles has been also investigated. Thus, the furans (14) were obtained on reacting the oxiranes (11) with malononitrile (cf. Scheme 2)[20]. However, trials for synthesis of furans via the reaction of other active methylene reagents with oxiranes have failed.




Scheme (2)

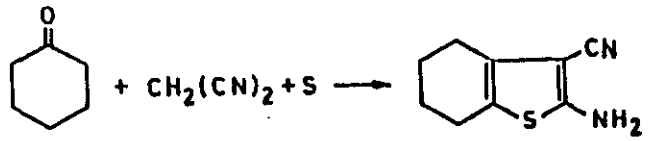
The conjugated addition of the anion of protected cyanohydrin (15) to β-nitrostyrene gives the adduct (16) in good yield (55-85 %). A mild hydrolysis of the latter yields nitrocyanohydrin (17), which can be converted into the furan derivative (18) (cf. Scheme 3)[21].




Scheme (3)

b. Synthesis of Thiophene and Condensed Thiophene Derivatives:

The most extensively utilized synthesis of thiophenes from nitrile compounds is Gewald synthesis[22]. Thus, heating the ketone, active *methylene nitrile and elemental sulphur in the presence of base as a catalyst* affords thiophenes[22]. For example, heating cyclohexanone, malononitrile and elemental sulphur in ethanolic triethylamine solutions affords 2-aminothiophene derivative (19) (cf. Eq. 3)[23-27].



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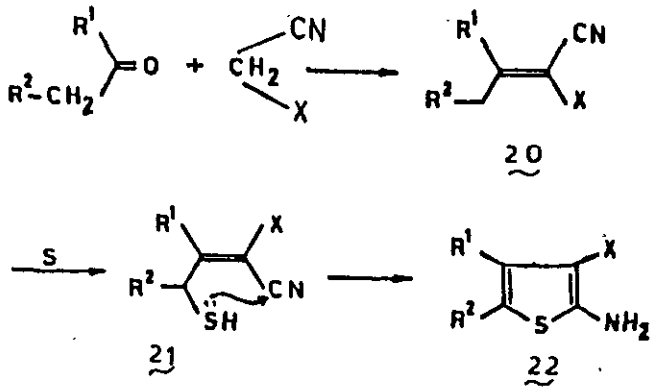
Eq·(3)

It is assumed that $\alpha,\beta$-unsaturated nitriles (20) are firstly formed. The 4-carbon in these nitriles reacts with elemental sulphur to yield an intermediate mercapto derivative (21), which cyclises into the final isolable thiophene derivative (22) (cf. Scheme 4)[23-27].



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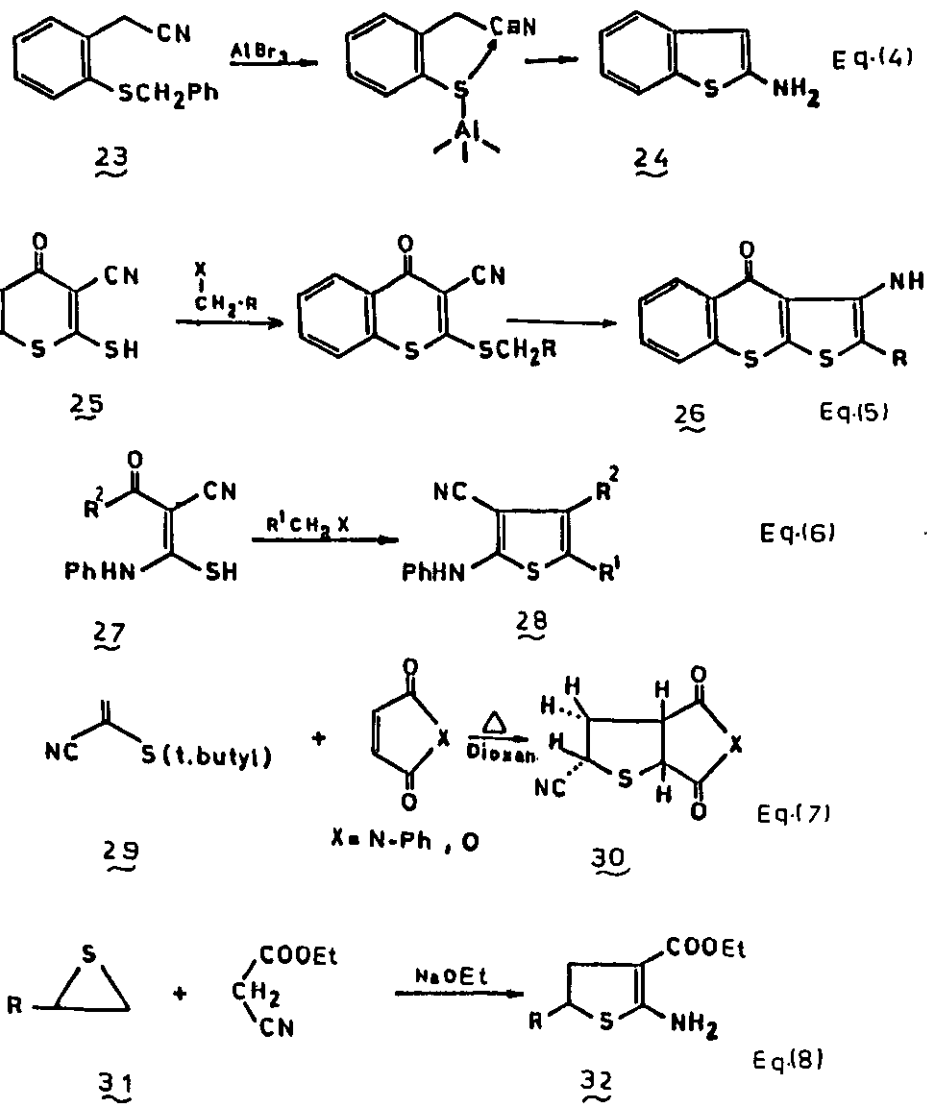
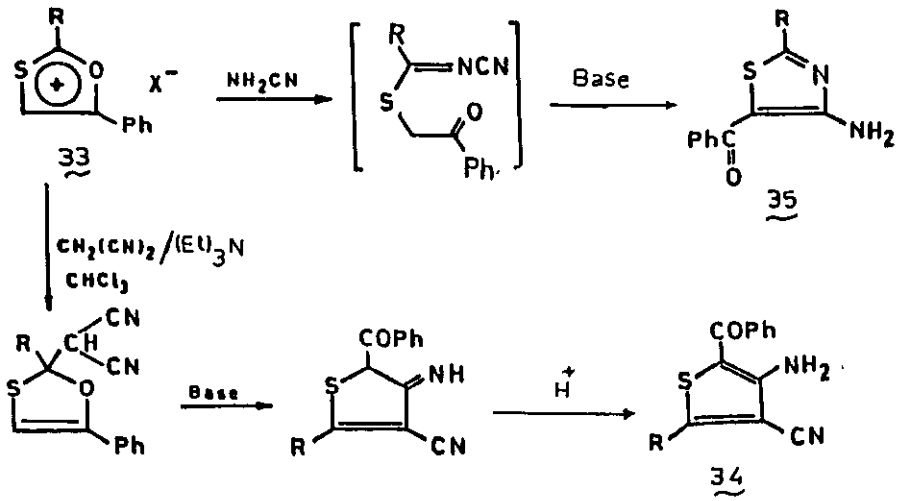
Scheme (4)

$\gamma$-Mercaptonitriles have been reported to undergo cyclisation into thiophene derivatives in the presence of an acid catalyst. For example, (23) cyclised into (24) on heating in the presence of $AlBr_3$ (cf. Eq. 4)[28-30]. Another similar synthesis that affords condensed thiophene derivatives 26 utilizing o-mercapto-cyano compounds as a starting component is the reaction of (25) with active methylene reagents (cf. Eq. 5)[31]. Also, the thioanilides of the type (27) react with active methylene reagents to yield the thiophene derivatives (28) (cf. Eq. 6)[32]. 2-tert-butylthioacrylonitrile (29) adds thermally to maleic anhydride or N-phenylmalimide in dioxan solution to yield the corresponding fused thiophenes (30) with loss of the tert-butyl group (cf. Eq. 7)[33]. Also the thiophene derivatives (32) are isolated in acceptable yields (30-40%) on reacting the thiranes (31) with ethyl cyanoacetate (cf. Eq. 8)[34].

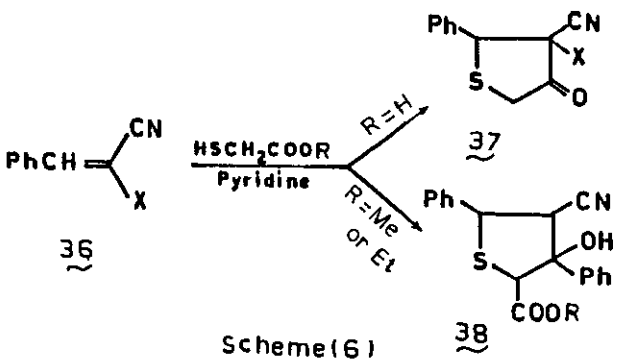



The reaction of oxathiolonium derivatives (33) with malononitrile in triethylamine-chloroform solution affords the aminothiophene derivatives (34). The reaction is believed to proceed via the sequence demonstrated in Scheme 5[35]. It is interesting to note that when cyanoamide was used instead of malononitrile, the thiazole derivatives (35) were isolated (cf. Scheme 5)[35].



Scheme(5)

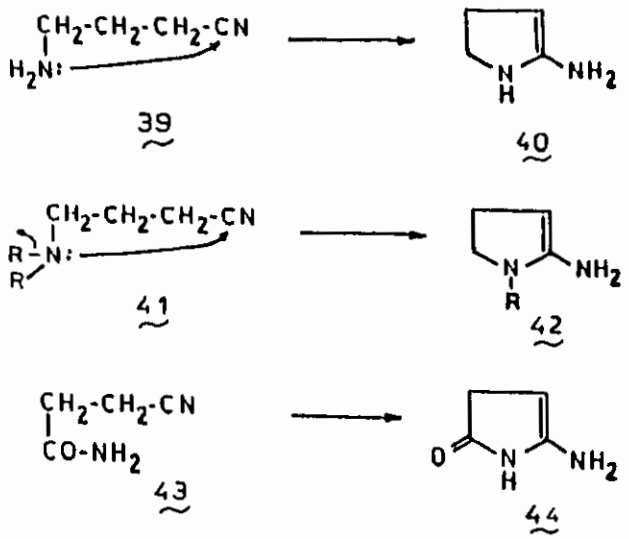
Formation of thiophenes on reacting the cinnamonitriles (36) with thioglycollic acid in pyridine has been reported almost simultaneously by Elnagdi et al.[36,37] and by Kambe et al.[38]. While the first group assumed structure (37) for the reaction product, the other group assigned structure (38) for the product of reaction of (36) where X = COPh with thioglycollic acid. In our opinion, it seems odd to believe that (38) did not dehydrate if it was the reaction end product (cf. Scheme 6).



Scheme(6)

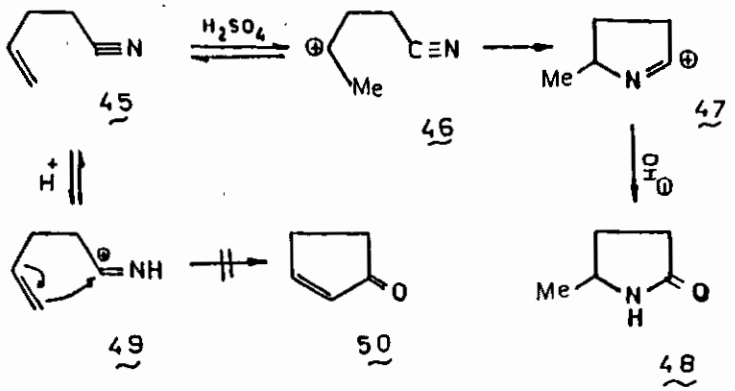
c. Synthesis of Pyrrole and Condensed Pyrrole Derivatives:

γ-Aminobutyronitrile (39) has long been known to cyclized into the pyrrole derivative (40) (cf. Scheme 7)[39-43]. When the nitrogen atom is tertiary as in (41) the cyclization proceed via dealkylation thus afford (42) (cf. Scheme 7)[39-43]. ω-Cyanocarboxamide (43) has sufficiently basic nitrogen to cyclize into pyrrolone. For example, cyclization of (43) affords the pyrrolone (44) (cf. Scheme 7)[39-43].



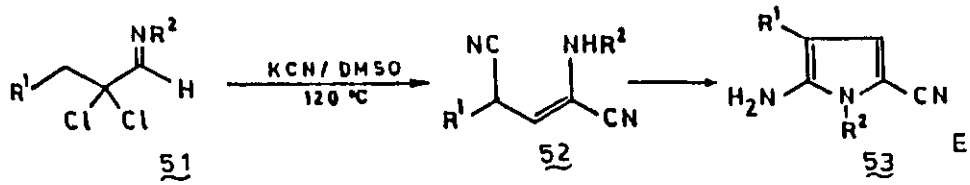
Scheme (7)

4-Pentenonitrile (45) affords, under typical Ritter reaction conditions, 5-methylpyrrolidin-2-one (48). The acyclic nitrilium salt (46) and the cyclic (47) can be considered as intermediates (cf. Scheme 8)[44,45]. It is of interest that, 2-cyclopentenone (50) derived from the carbocation (49) did not form eventhrough a similar cyclization process which was reported when cyclic rings to be formed contain more than six atoms (cf. Scheme 8)[44,45].



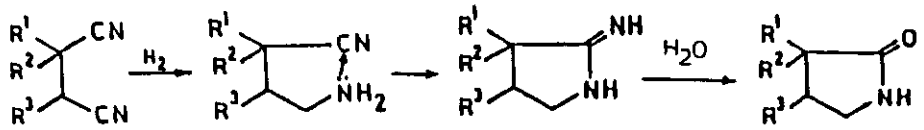
Scheme (8)

Dinitriles (52) formed via reaction of (51) with cyanides in dimethylsulphoxide at 120°C afford the pyrrole derivatives (53) (cf. Eq. 9)[46]. Similarly the dinitriles of the type (54) were cyclized into pyrrolidines (55) through reductive cyclization step. The reaction is assumed to proceed via the sequence demonstrated in Eq. 10[47-49].




51 52 53

Eq·(9)



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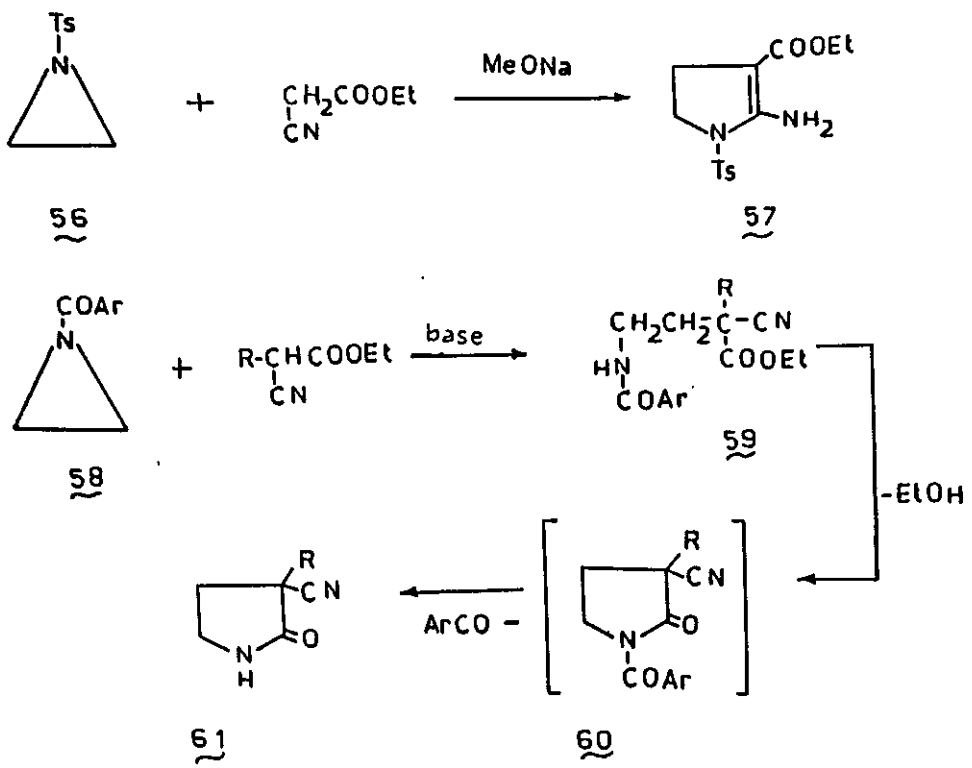
Eq·(10)

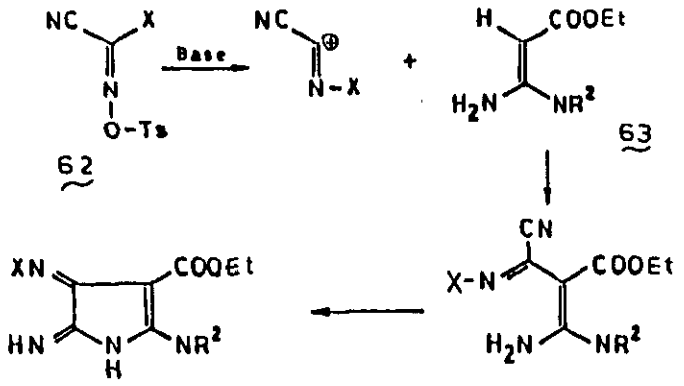
N-Tosylaziridine (56) reacts with ethyl cyanoacetate in sodium methoxide to afford the N-tosylamino-pyrrole derivative (57) (cf. Scheme 9)[50]. In contrast, Stamm[51] reported that N-aroylaziridines (58) afford the acyclic derivatives (59) on treatment with ethyl alkylcyanoacetate. Moreover, cyclisation of (59) afford the cyano ketones (61) via intermediacy of (60) (cf. Scheme 9)[51].




56 57 58 59 60 61

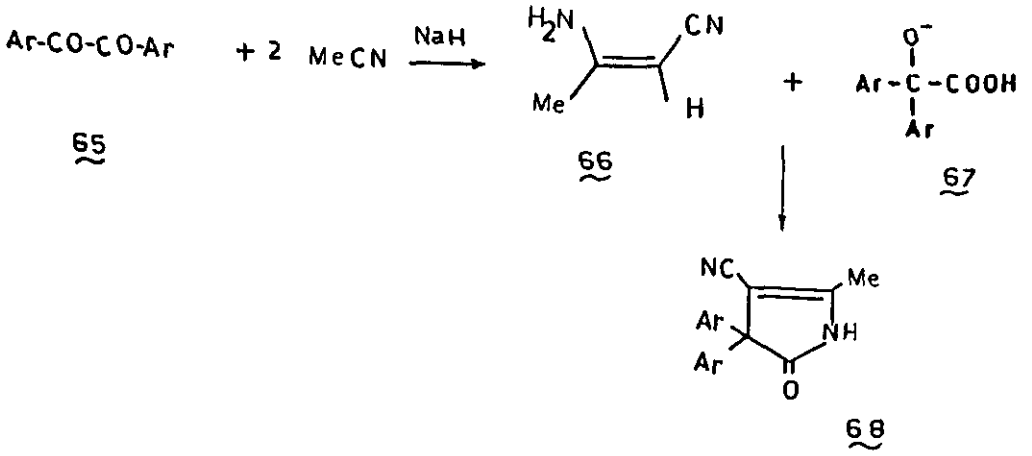
Scheme (9)

Similarly, reaction of the tosylates (62) with the enaminoesters (63) affords the pyrrole derivatives (64). The unexpected formation of (64) can be exaplained in terms of a base catalysed Beckman rearrangement of (62) (cf. Scheme 10)[52].



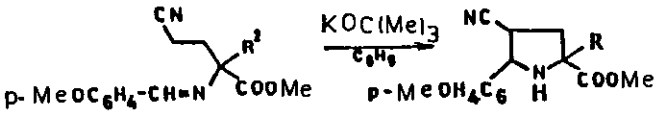

Scheme (10)

Treatment of benzils (65) with sodium hydride in acetonitrile afford the pyrrole derivatives (68). The formation of (68) may be assumed to proceed via the reaction of 2-aminocrotonate (66), resulting from dimerisation of acetonitrile, with benzilic acids (67), the latter results from rearrangement of (65) under the reaction conditions (cf. Scheme 11)[49].

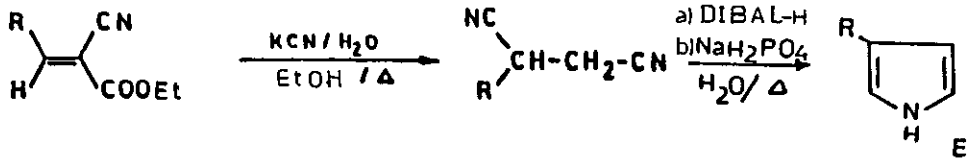



Scheme (11)

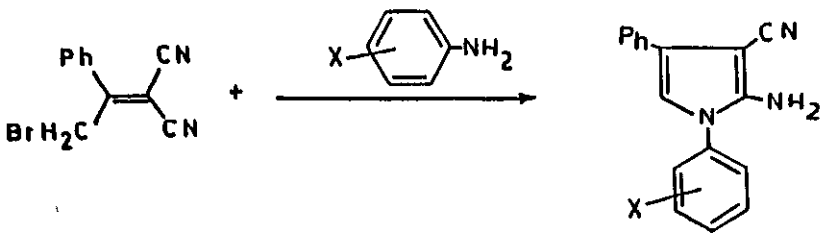
Recently, several syntheses of pyrrole derivatives utilizing organic cyano compounds as a starting components were reported[53-60], the most interesting results of which are demonstrated in the Equations below[61-65] (cf. Eqs. 11-16).



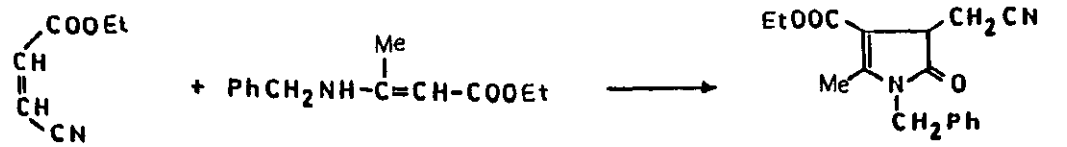
Eq.(11)



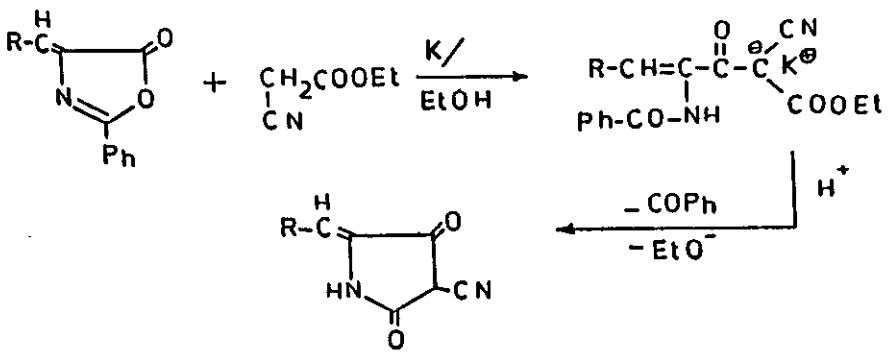
Eq.(12)



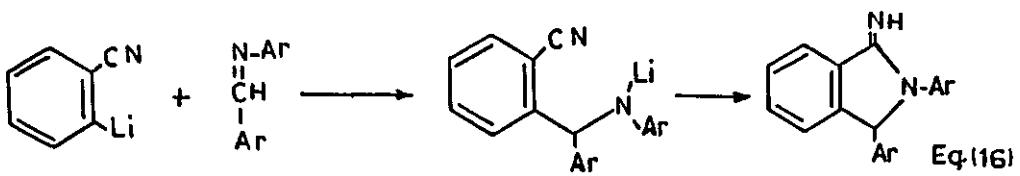
Eq.(13)



Eq.(14)

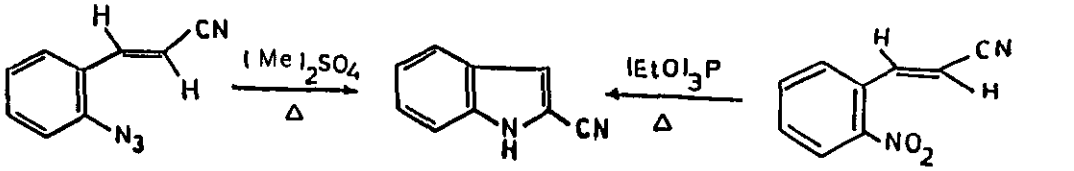


Eq. (15)



Eq.(16)

Several indole syntheses were reported[66-70]. As a demonstrating example, heating o-azidocinnamonitrile (69) in dimethylsulphoxide at 140°C affords 2-cyanoindole (70) (cf. Eq. 17)[71]. The latter could also be obtained on heating o-nitrocinnamonitrile (71) in triethylorthophosphate at 160°C (cf. Eq. 17)[72].

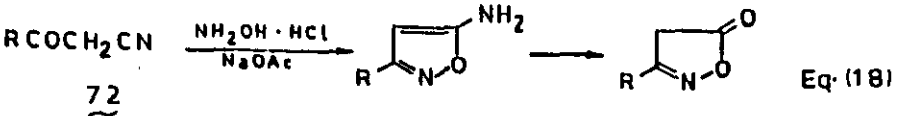



69 70 71 Eq.(17)

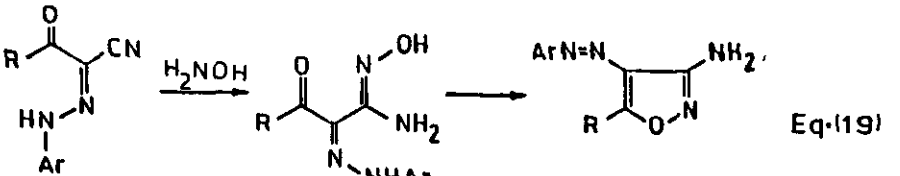
2. Synthesis of Five-Membered Rings with Two Hetero-Atoms:

a. Synthesis of 1,2-Oxazoles and 1,3-Oxazoles:

β-Functional nitriles and α,β-unsaturated nitriles are extensively utilized for synthesis of 1,2-oxazoles[73-76]. For example, β-oxonitriles (72) are reported to react with hydroxylamine hydrochloride in the presence of sodium acetate to afford 5-amino-1,2-oxazoles (73) (cf. Eq. 18)[77]. In contrast to this, Elnagdi et al.[78] and other Italian group [79] have reported, that the arylhydrazones of β-oxonitriles or β-ketoesters (74) react with hydroxylamine to afford amidoximes (75), which cyclized under acidic conditions to yield isomeric, otherwise difficult accessible, 3-amino-1,2-oxazoles (76) (cf. Eq. 19). The Italian group has attributed the difference in the behaviour of the β-cyanoacetic esters with their arylhydrazone derivatives to the decrement in reactivity of the ester group due to hydrogen bonding. However, Elnagdi et al. have



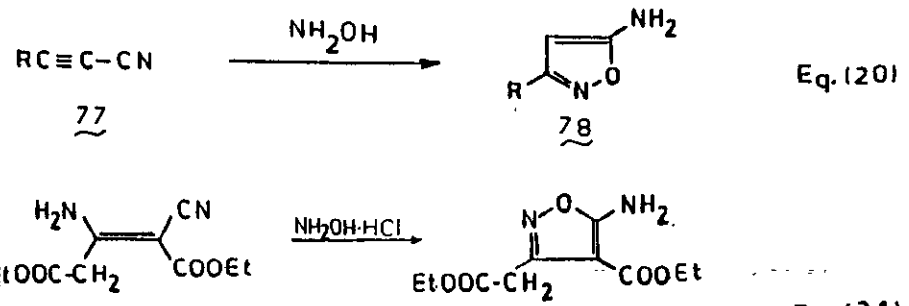

72 73 Eq.(18)




74 75 76 Eq.(19)

attributed this difference to protonation in acidic media. Evidence in favour of this point of view was the observed inactivity of the hydrazones towards hydroxylamine in alkaline media and the formation of 5-amino-1,2-oxazoles on conducting the reaction in sodium methoxide[80]. It is believed that, both factors discussed by both groups play a role.

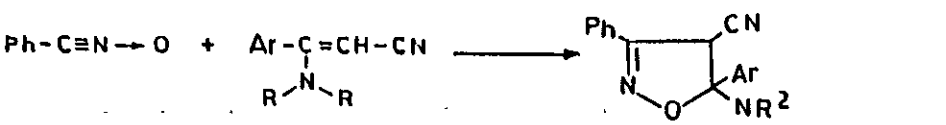
α,β-Acetylinic nitriles (77) react with hydroxylamine to afford 5-amino-1,2-oxazoles (78) (cf. Eq. 20)[81]. Other interesting examples of 1,2-oxazole synthesis utilizing nitriles as starting components are shown below (cf. Eqs. 21-23)[82-84].



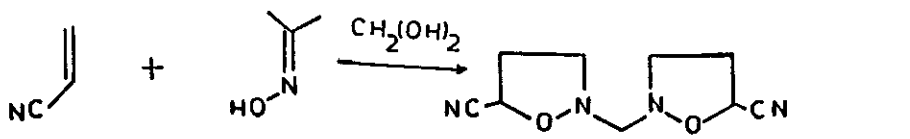

77 78 Eq. (20)




Eq. (21)

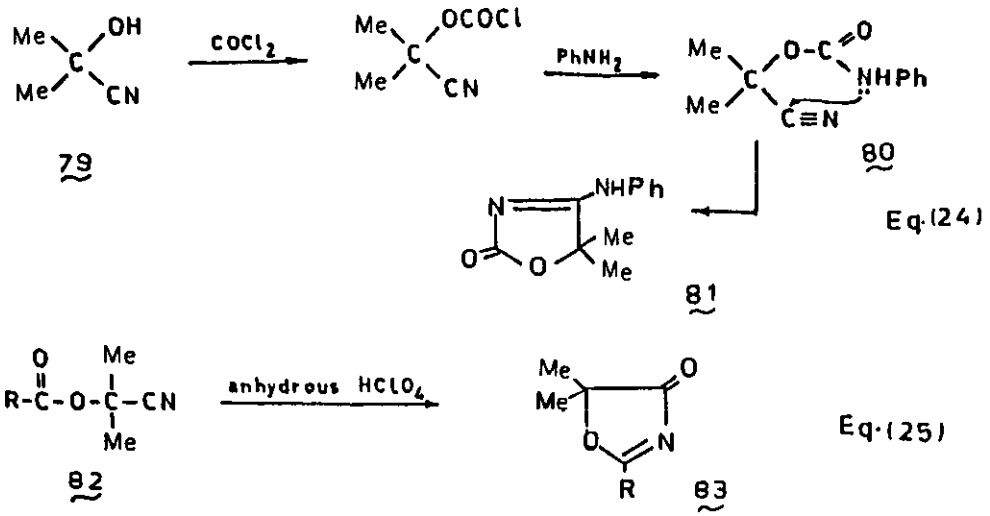



Eq. (22)




(Major) Eq. (23)

Cyanohydrins could be converted into amino-1,3-oxazolones. Thus, when acetonecyanohydrin (79) was treated with phosgen followed by aniline, the 4-(phenylamino)-1,3-oxazolo-2-one derivative (81) was isolated[85] and not the carbamate derivative (80) which was claimed earlier for the reaction product[86] (cf. Eq. 24). In a similar manner, acylated cyanohydrins (82) were converted into 1,3-oxazolin-4-one derivatives (83) (cf. Eq. 25)[87].

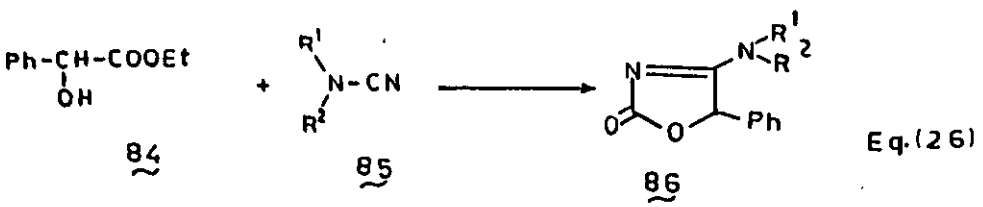


Eq.(24)



Eq.(25)

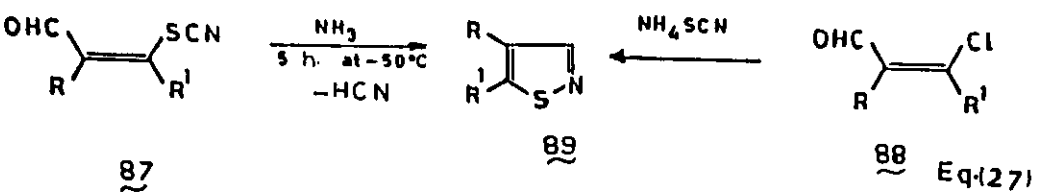
The condensation of ethyl mandelate (84) with dialkylcyanamides (85) were reported to afford the 1,3-oxazol-4-one derivatives (86) (cf. Eq. 26)[88,89].



Eq.(26)

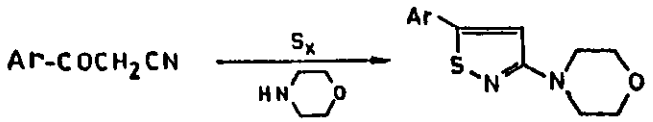
b. Synthesis of 1,2-Thiazoles and 1,3-Thiazoles:

1,2-Thiazoles (89) are prepared via reacting the E or Z isomers (87) with ammonia or via refluxing the E or Z isomers of (88) with ammonium thiocyanate (cf. Eq. 27)[90,91].

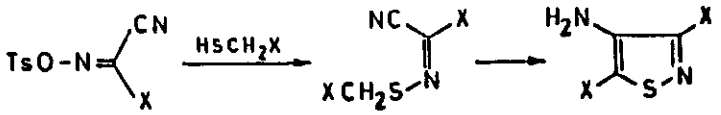


Eq.(27)

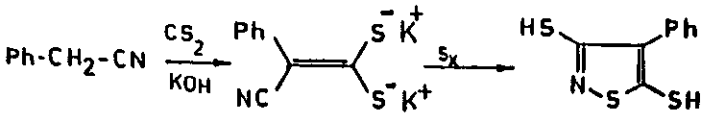
Other synthetic approaches of 1,2-thiazoles utilizing nitriles as starting components are summarized below (cf. Eqs. 28-31)[92-96].



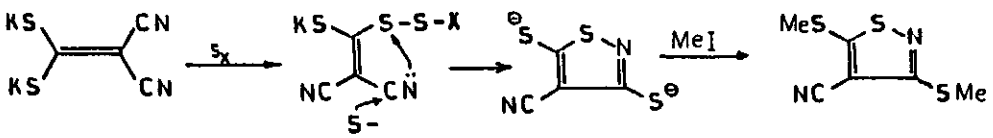
Eq.(28)



Eq.(29)

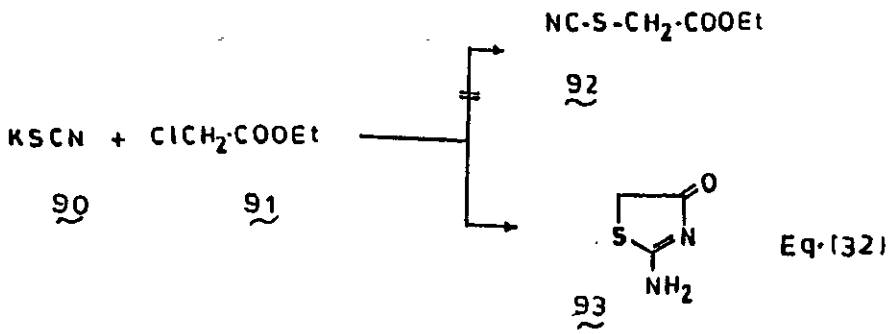


Eq.(30)



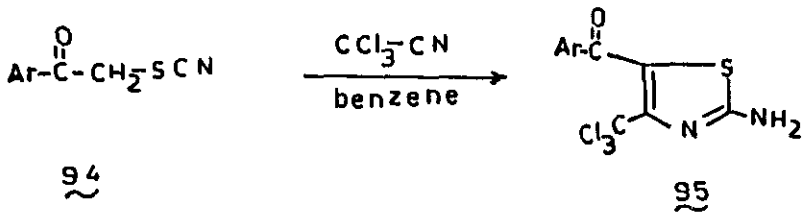
Eq.(31)

Nitriles were utilized for more than a century and, up till now, for the synthesis of 1,3-thiazoles[97-120]. Thus, Heintz (1865) reported the reaction of potassium thiocyanate with ethyl chloroacetate[97]. Although the reaction product was firstly thought to be ethyl thiocyanatoacetate (92), it proved to be peseudothiohydantoin (93) (cf. Eq. 32). Recently Elnagdi et al.[121] successfully prepared the 2-amino-1,3-thiazole



Eq.(32)

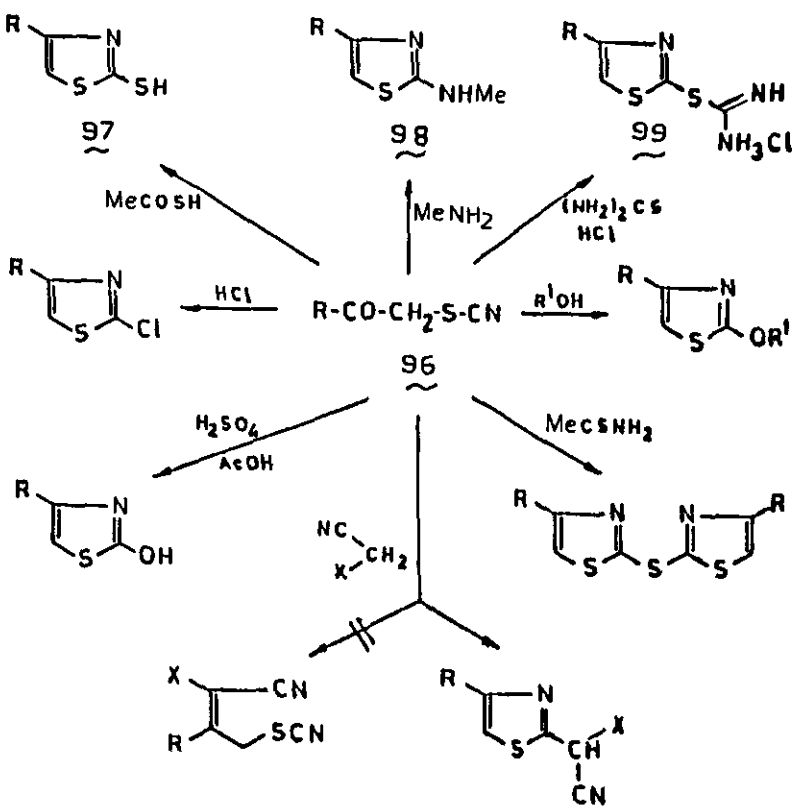
derivatives (95), which are expected to be of biological and medicinal importance, via reacting the thiocyanatoketones (94) with trichloroacetonitrile (cf. Eq. 33).



Eq. (33)

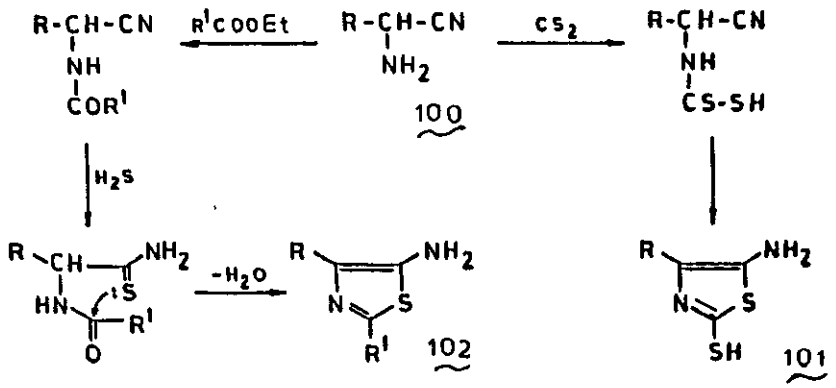
94 95

Thiocyanatoketones (96) were also converted into 1,3-thiazoles on reaction with a variety of reagents[122-127]. Thus, for examples, it reacted with thioacids to afford 2-mercaptothiazoles (97); with amines to afford the aminothiazoles (98), and with thiourea to afford the thiazoles (99) (cf. Scheme 12).



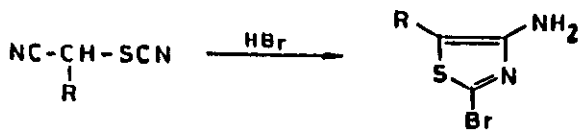
Scheme (12)

Aminoacetonitrile derivatives (100) could be converted into 1,3-thiazoles (101)-(102) via the sequences shown in Scheme 13[128-130].

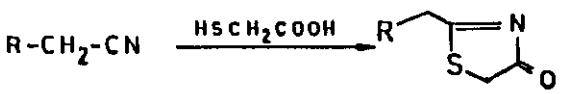


Scheme (13)

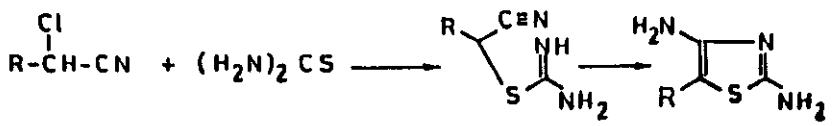
Other interesting thiazole syntheses, utilizing nitriles as starting components are shown in the equations below (cf. Eqs. 34-37)[131-134].



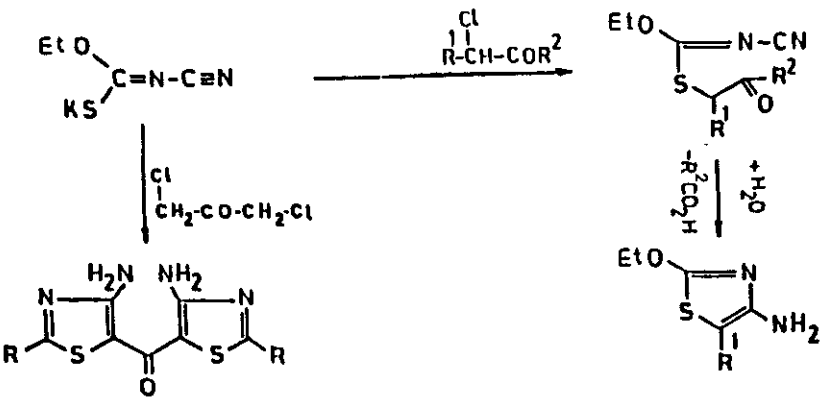
Eq. (34)



Eq. (35)



Eq. (36)

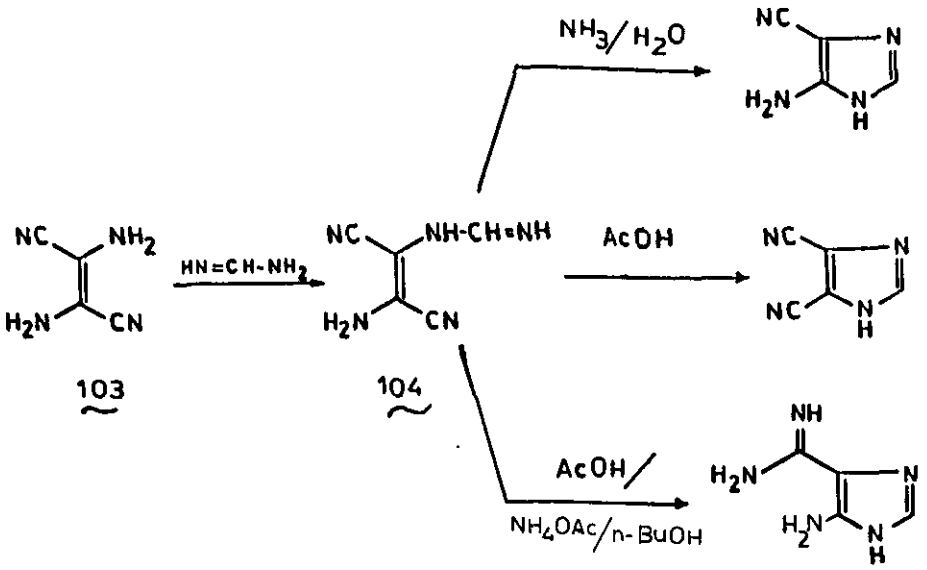


Eq. (37)

c. Synthesis of Pyrazoles and Imidazoles:

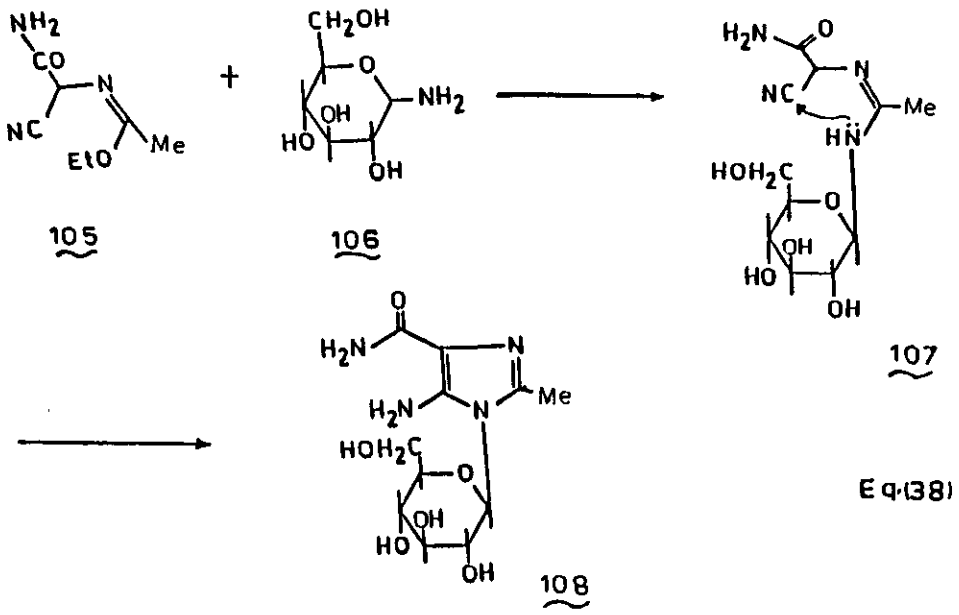
The recent development in the synthesis of pyrazole derivatives utilizing nitriles as starting components has been efficiently reviewed very recently by Elnagdi et al.[135]. Consequently, in our review article, no more emphasis on this topic will be offered.

2,3-Diaminodinitrile (103) has been recently utilized for the synthesis of imidazole derivatives. Thus, (103) reacted with formamidine to yield (104) which could be cyclized under different conditions to yield different imidazole derivatives (cf. Scheme 14)[136-140].




Scheme (14)

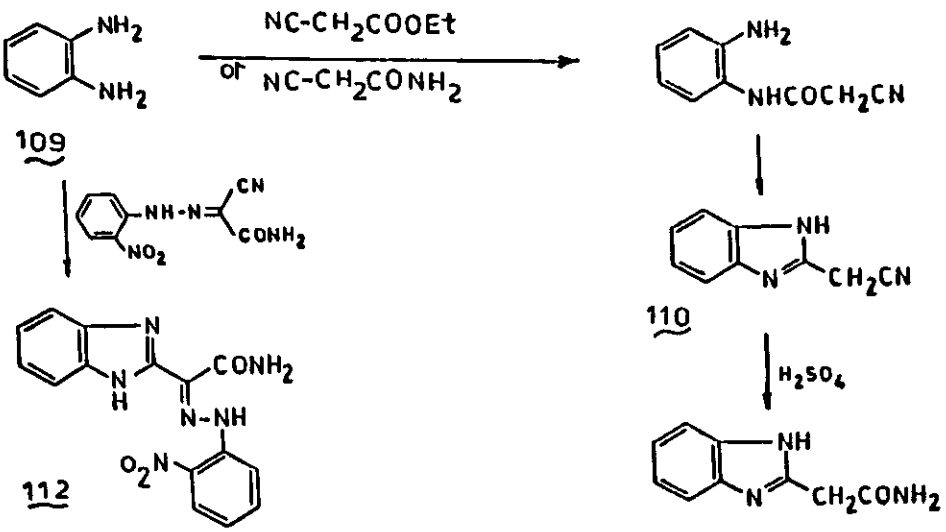
Smith and Yates[141] have reported a useful process leading to imidazole nucleosides. Thus, the adenine derivative (108) could be synthesised from the iminoester (105) and D-xylopyranosylamine (106) via intermediacy of the cyanoimidate (107) (cf. Eq. 38).



105 106 107 108

Eq.(38)

The reaction of o-phenylenediamine (109) with ethyl cyanoacetate or cyanoacetamide has been reported to afford 2-cyanomethylbenzimidazole (110)[142-143]. However, the 2-nitrophenylhydrazo derivatives of cyanoacetamide afforded the hydrazone derivative (112) when reacted with o-phenylenediamine (cf. Scheme 15)[144]. The carboxamide derivative (111) was formed when o-phenylenediamine and cyanoacetamide were reacted at 40-50°C in presence of concentrated sulphuric acid (cf. Scheme 15)[143].



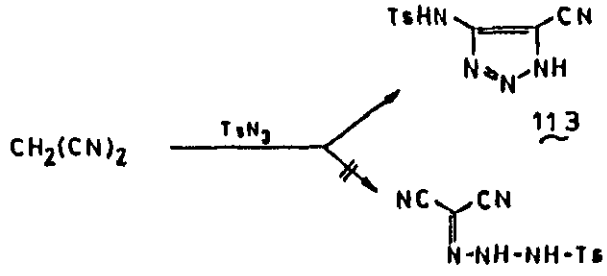
109 110 111 112

Scheme(15)

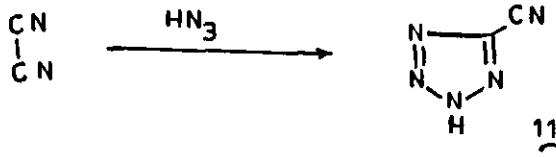
3. Synthesis of Five-Membered Rings with Three Hetero-Atoms:

a. Synthesis of 1,2,3-Triazoles and 1,2,4-Triazoles:

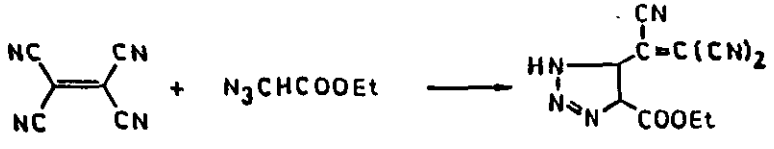
Elnagdi et al.[145] have sufficiently previously reviewed the 1,2,3-triazoles syntheses via the reaction of acyclic and heterocyclic diazo compounds with nitriles. Consequently, only few specific examples for the 1,2,3-triazoles syntheses will be demonstrated. For examples, malononitrile reacts with tosyl azide to afford 4-tosylamino-5-cyano-1,2,3-triazole (113) (cf. Eq. 39)[145-148]. Similarly the reaction of cyanogen with hydrazoic acid can be controlled to give the 5-cyano-1,2,3,4-tetrazole (114) (cf. Eq. 40)[149-151]. Also, ethyl azidoacetate reacts with tetracyanoethylene to afford 1,2,3-triazole derivative (115) (cf. Eq. 41)[152].




Eq. (39)

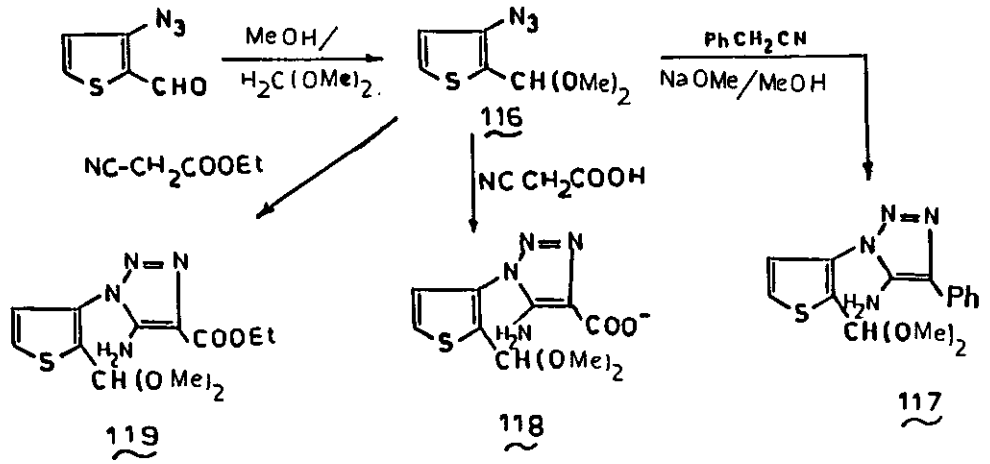



Eq. (40)




Eq. (41)

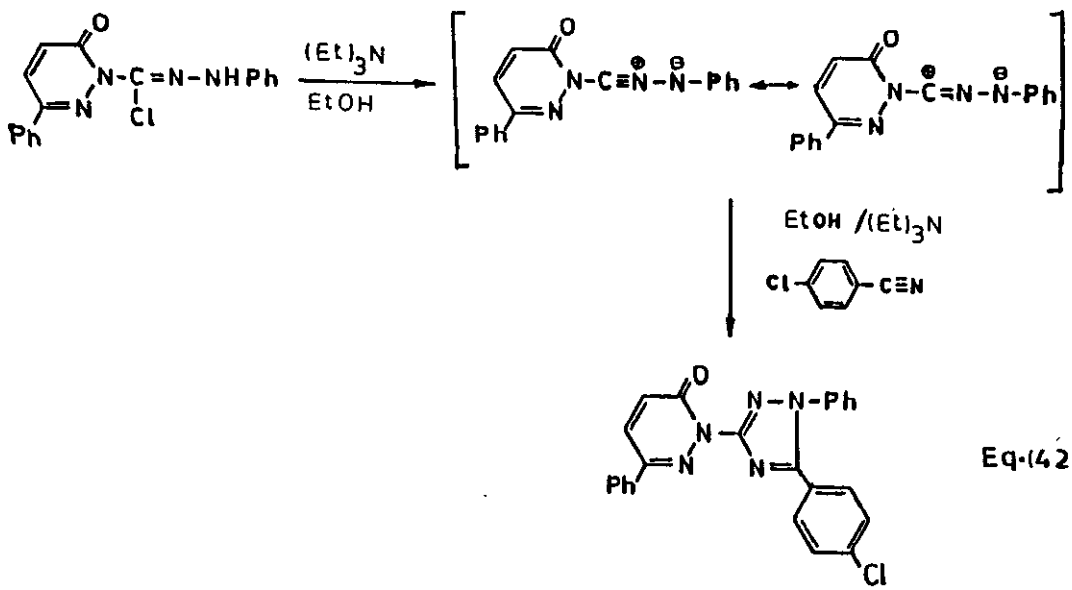
The azidothiophene derivative (116) reacts with nitriles to yield 1,2,3-triazoles (117-119) as demonstrated in the Scheme below (cf. Scheme 16)[153].



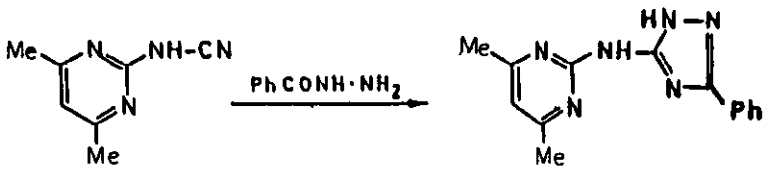
Scheme (16)

The utility of nitriles for syntheses of 1,2,4-triazoles has been efficiently surveyed in a monograph on the chemistry of 1,2,4-triazoles[154]. Consequently we are going here to undertake only the reported examples on this subject that were not surveyed earlier.

The reaction of nitrile imines with nitriles has long been known to afford 1,2,4-triazoles. A recent interested application of this synthetic approach is shown below (cf. Eq. 42)[155]. Also the cyclocondensation of the nitrile (120) with benzoylhydrazine affords the 1,2,4-triazole derivative (121) (cf. Eq. 43)[156].

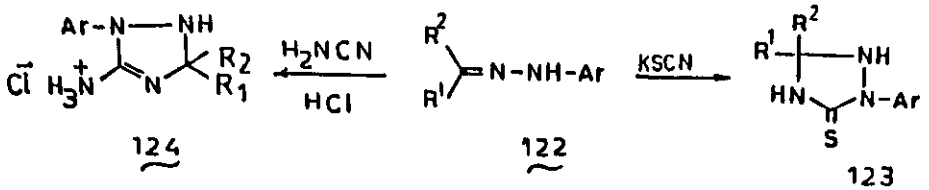


Eq.(42)



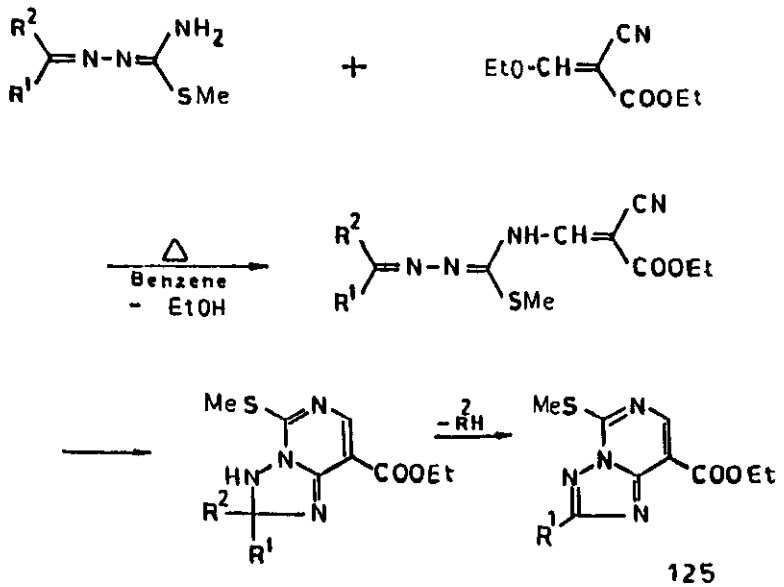

120 121 Eq. (43)

The reaction of ketone arylhydrazones (122) with potassium thiocyanate in acidic media affords the corresponding 1,2,4-triazolidin-5-thiones (123)[157,158]. Also cyanamide reacts with ketone arylhydrazones to yield the 5-amino-1,2,4-triazoline hydrochloride (124) (cf. Eq. 44)[157,158].




124 122 123 Eq. (44)

An example for the synthesis of condensed 1,2,4-triazoles (125) utilizing nitriles as starting components is shown below (cf. Scheme 17)[159].




125

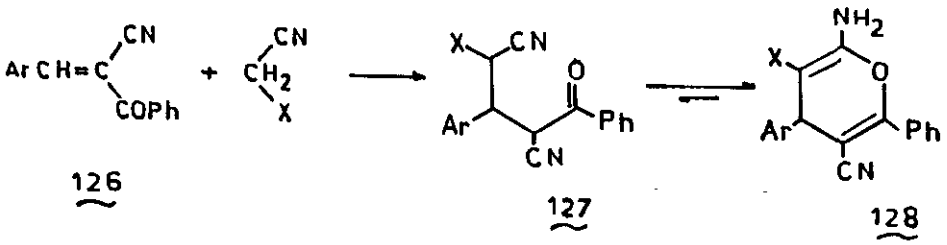
Scheme (17)

ii. Synthesis of Six-Membered Heterocycles:

1. Synthesis of Six-Membered Rings with One Hetero-Atom:

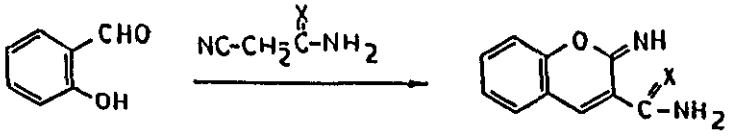
a. Synthesis of Pyrans, Coumarins and Condensed Pyrans:

A variety of pyrans, coumarins and condensed pyrans were prepared recently utilizing nitriles as a starting materials[160-165]. ∝ -Cyanochalcones (126) react with active methylene reagents e.g. malononitrile and ethyl cyanoacetate to yield the corresponding Michael adducts (127)[166,167]. These were proved later by $^1$H NMR to exist mainly in the cyclic pyran form (128) (cf. Eq. 45)[168]. Ring chain tautomerism was suggested to account for the conversion of (127) into (128) on reflux in ethanolic-piperidine solutions[168].

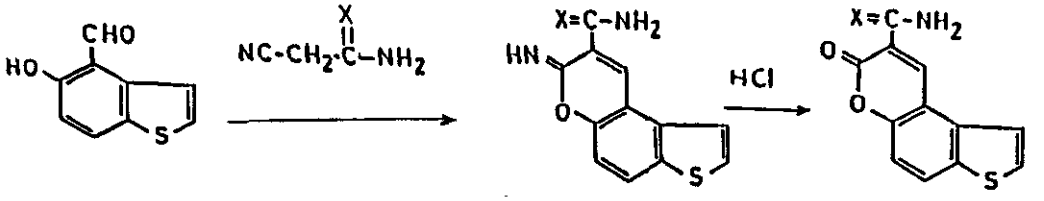



126 127 128 Eq.(45)

Generally, coumarin derivatives (129, 130) are synthesised on condensing o-hydroxyaldehydes with nitrile containing compounds e.g. cyanoacetamide or cyanothioacetamide. Examples are summarized below (cf. Eqs. 46, 47)[169-173].



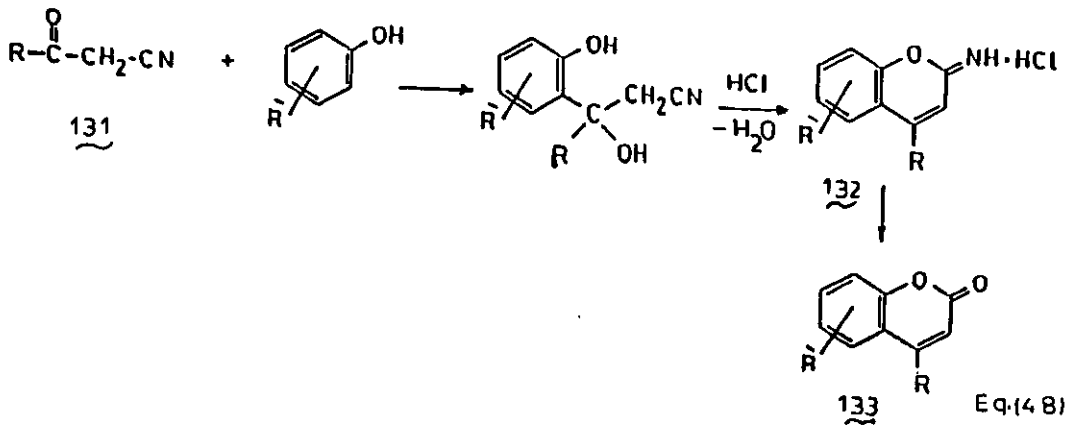

Eq.(46)




X = O; S

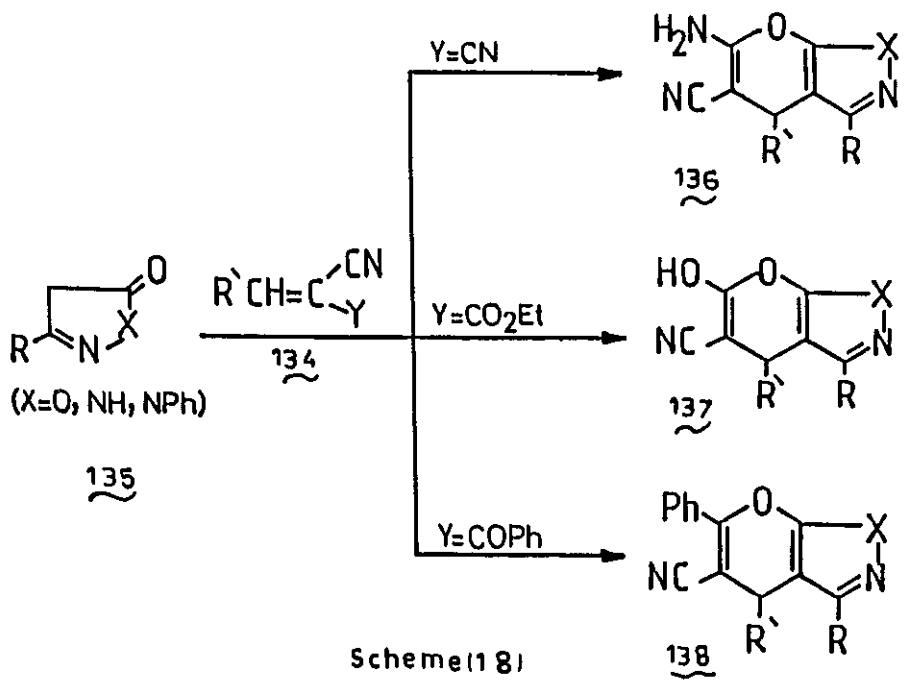
Eq.(47)

Acylacetonitrile condenses with polyhydric phenols, such as resorcinol in the presence of concentrated sulphuric acid to yield the corresponding coumarin derivatives[174-177]. For example, Sato and Amakasu[178] have shown that benzoylacetonitrile (131; R = Ph) or acetylacetonitrile (131; R = $CH_3$) undergo a carbon to carbon condensation with m- and p-substituted phenols in the presence of dry hydrogen chloride gas to afford the corresponding imino coumarins (132) and/or coumarins (133) (cf. Eq. 48).



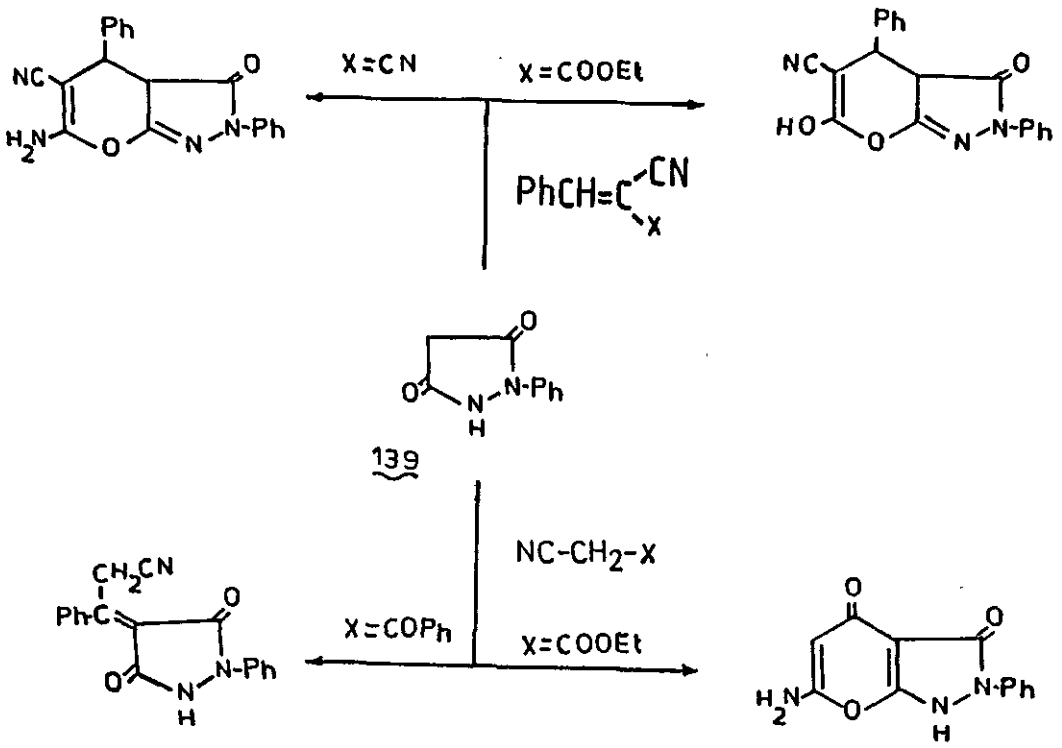
Eq.(48)

The cinnamonitrile derivatives (134) react with pyrazolones (135; X = NH, NPh) or isoxazolin-5-ones (135; X = O) to yield the corresponding pyranopyrazoles or pyranoisoxazoles (136-138) respectively (cf. Scheme 18)[179-181].



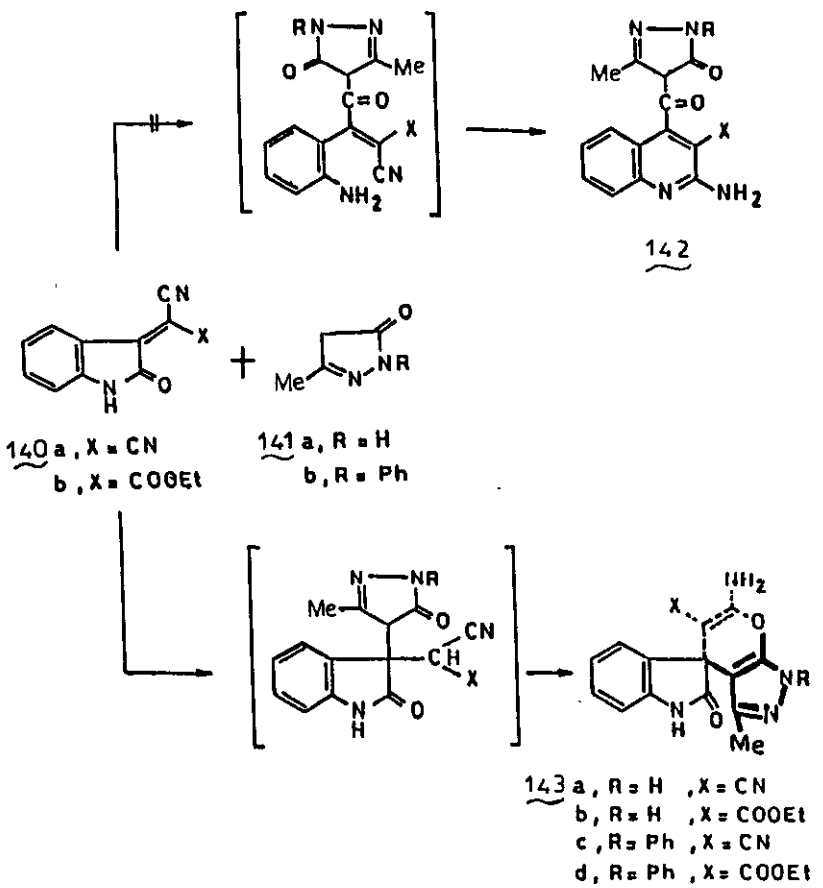
Scheme(18)

1-Phenyl-pyrazoline-3,5-dione (139) reacts with activated nitrile derivatives to yield several pyrano[2,3-c]-pyrazoles (cf. Scheme 19)[182]. Similarly, 1,3-diphenylthiohydantoin, thiazolidine-diones, thiazolidine-dithiones and isorhodanine react with cinnamonitriles to yield the corresponding pyranoazole derivatives. However, in some cases, ylidene group exchange took place[182].




Scheme (19)

Although the reaction of 3-cyanomethylene-isatin derivatives (140a,b) with 3-methyl-2-pyrazolin-5-one derivatives (141a,b) were reported to afford 4-azoloyl-2-aminoquinolines (142)[183]. Recent investigations utilizing high resolution $^{1}H$ NMR and $^{13}C$ NMR indicated that the structures of the reaction products are really the spiropyranylindolone derivatives (143a-c) (cf. Scheme 20)[184].

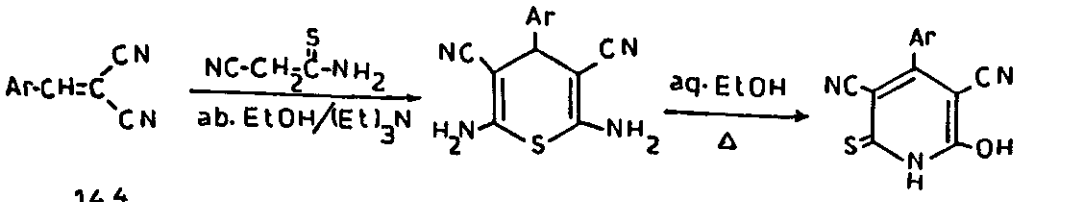



Scheme (20)

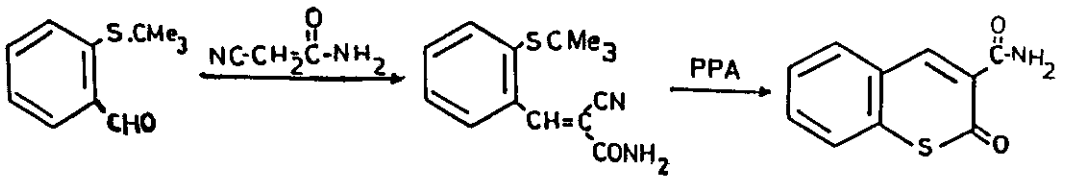
b. Synthesis of Thiopyrans and Thiocoumarins:

It has been shown via chemical routes and inspection of the high resolution $^{1}H$ NMR and $^{13}C$ NMR spectra that the thiopyrans (145) are the products of reaction of (144) with cyanothioacetamide in ethanolic-triethylamine solutions (cf. Eq. 49)[185]. Compounds (145) rearrange on heating in aqueous ethanol into the more stable dihydropyridines (146) (cf. Eq. 49)[185]. Previously reported formation of dihydropyridones[186] seems unlikely in the light of the present evidences.

Cyanoacetamide condensed with o-substituted benzaldehyde derivative (147) to afford the thiocoumarinone derivative (149). This is assumed to proceed via intermediacy of (148) (cf. Eq. 50)[187].



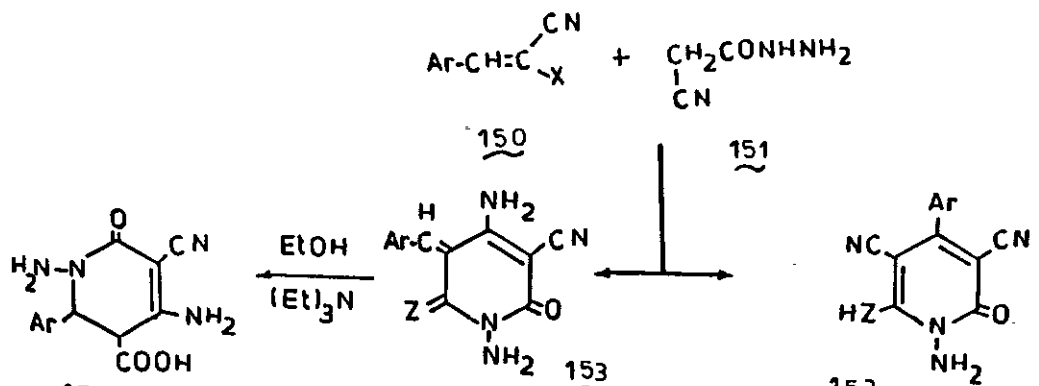
144 145 146 Eq.(49)



147 148 149 Eq.(50)

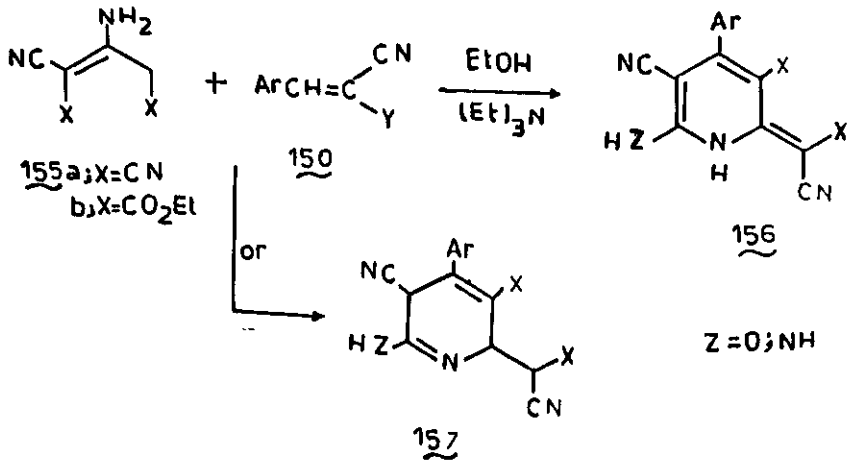
c. Synthesis of Pyridines, Quinolines, Isoquinolines and Condensed Pyridines:

Several pyridine, quinoline, isoquinoline and condensed pyridine syntheses, utilizing nitriles as starting components have been reported. However, this topic has been previously reviewed[2-6]. Consequently, only the recent reports in these area will be reported here. Thus, the cinnamonitriles (150) react with cyanoacetic acid hydrazide (151) to afford N-aminopyridones. Soto et al.[188] reported the direct formation of (152) as sole reaction product on heating (150) with (151) for 5 min. However, Elmoghayar et al.[190] have reported that the product previously identified as (152) is really (153) which rearranges on refluxing in aqueous ethanolic-triethylamine solutions into (154) (cf. Scheme 21). Evidences afforded on this problem are not conclusive and further investigations seem to be mandatory.

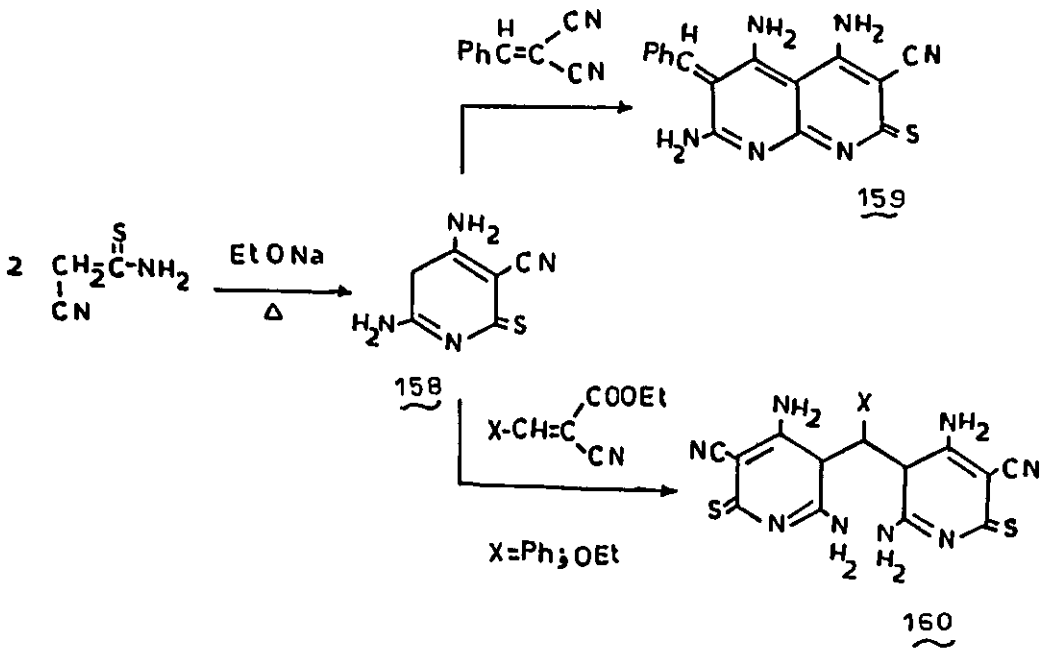


Scheme (21)

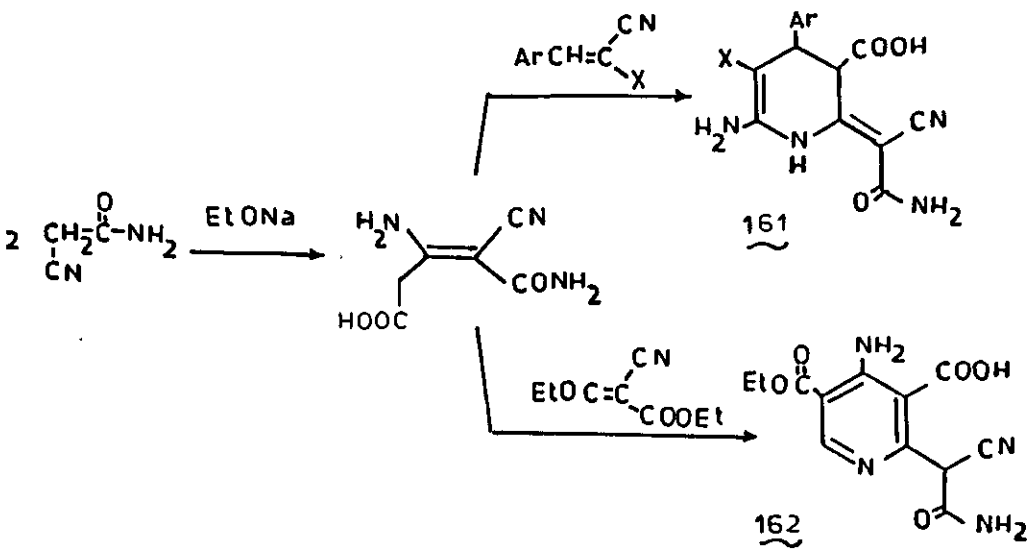
The reaction of the dimers (155a,b) with cinnamonitriles (150) in ethanolic-triethylamine solutions affords the pyridine derivatives (156, 157) (cf. Scheme 22)[191,192]. Recently, this approach has been explored for synthesis of several pyridine derivatives (158-162) (cf. Schemes 23, 24)[193-196].




Scheme (22)

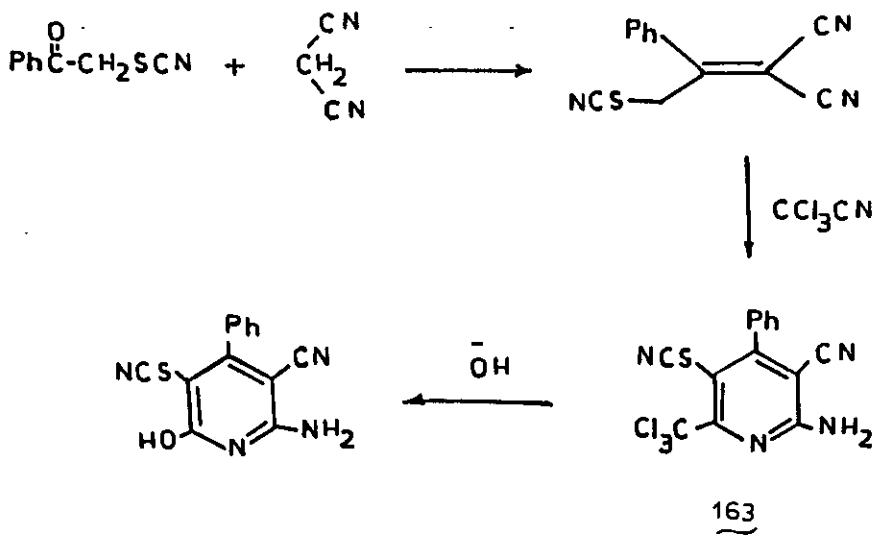



Scheme (23)



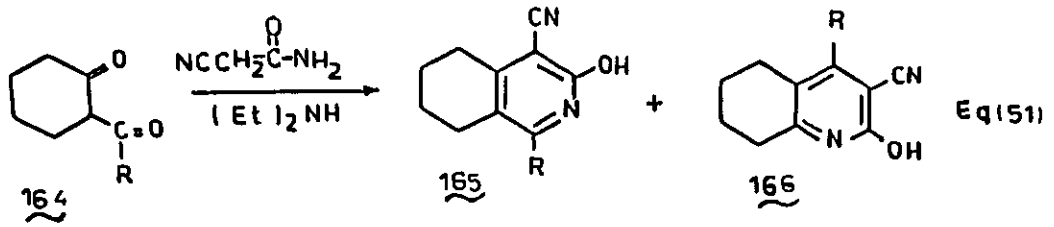
Scheme (24)

An interested pyridine synthesis is outlined via the sequence demonstrated in Scheme 25[197].



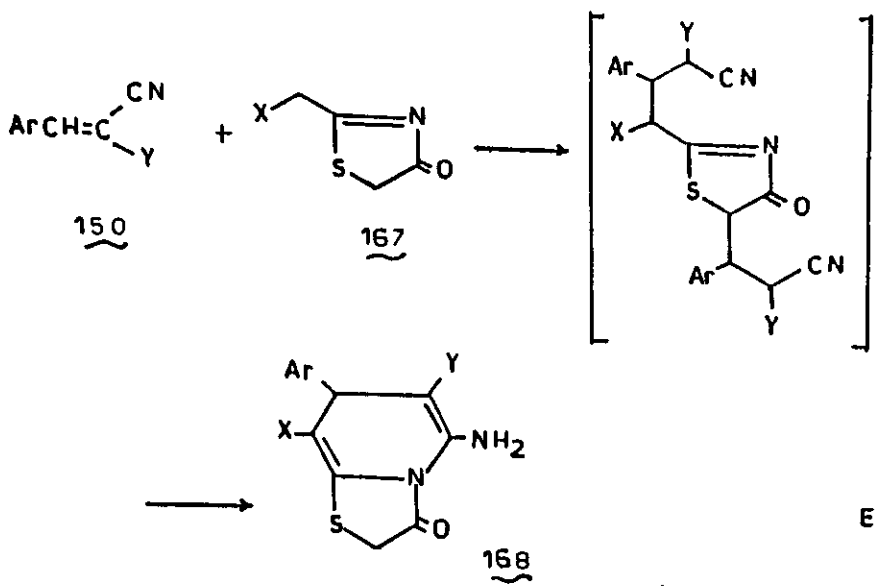
Scheme (25)

The condensation of 2-acylcyclohexanones (164) with cyanoacetamide in the presence of diethylamine results in a mixture of the isoquinoline derivatives (165) and the quinoline derivatives (166) (cf. Eq. 51)[198-202].




164 165 166 Eq(51)

A route for the synthesis of thiazolo[2,3-a]pyridines (168) from the reaction of 2-functionally substituted 2-thiazolin-4-one (167) with cinnamonitriles (150) has been reported simultaneously and independently by Elnagdi et al.[203] and Kambe et al.[204] (cf. Eq. 52).

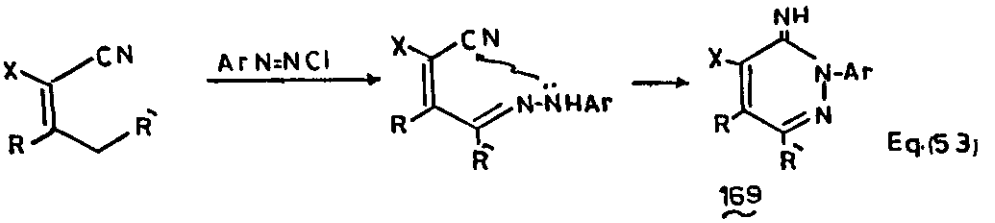



150 167 168 Eq.(52)

2. Synthesis of Six-Membered Rings with Two Hetero-Atoms:

a. Synthesis of Pyridazines and Condensed Pyridazines:

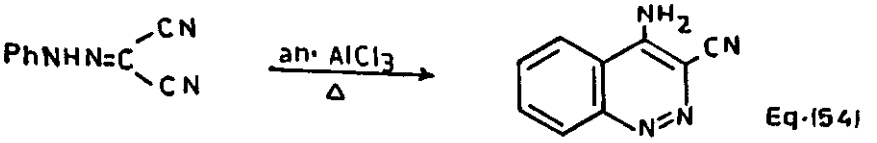
Recently, an interesting approach for synthesis of pyridazines (169) has been achieved[205]. This synthetic approach is summarized below (cf. Eq. 53).




169

Eq.(53)

Cinnoline derivatives were also reported utilizing ∝-hydrazononitriles as starting components. Thus, heating phenylhydrazonomalononitrile (170) with anhydrous $AlCl_3$ affords 4-amino-3-cyanocinnoline (171) (cf. Eq. 54)[206].



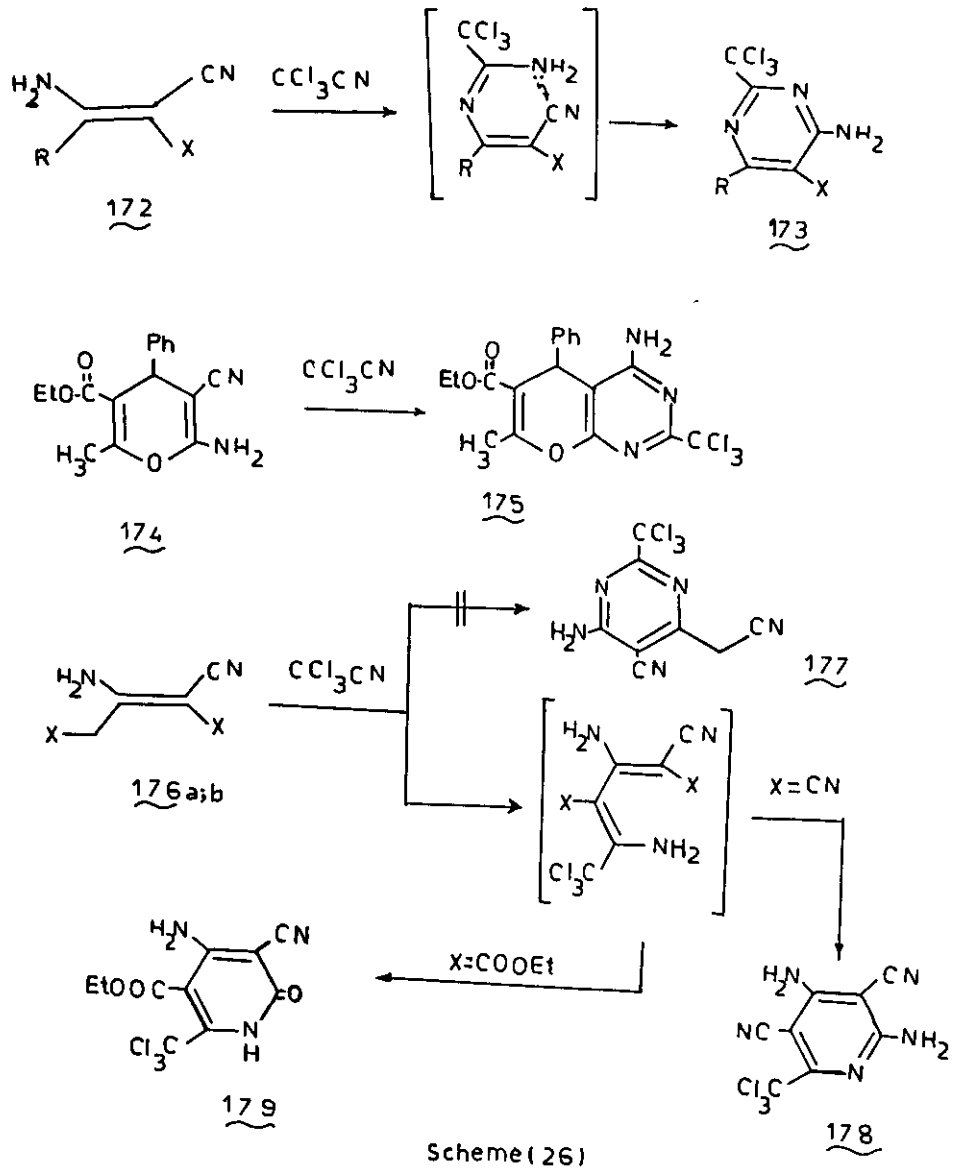

170

171

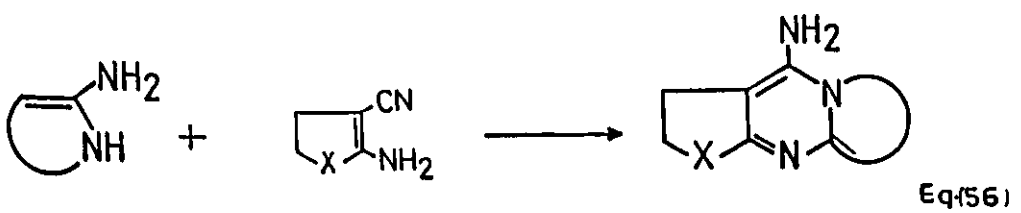
Eq.(54)

b. Synthesis of Pyrimidines and Condensed Pyrimidines:

A variety of pyrimidines synthesis, utilizing nitriles as starting components has been reported. The previously reviewed literature reports[1,4,207-211] will not be discussed here. Enaminonitriles (172) and (174) react with trichloroacetonitrile to yield the corresponding pyrimidine derivatives (173) and (175) respectively (cf. Scheme 26)[212-214]. Although (176a,b) has been reported to react with the same reagent to afford pyrimidine derivatives (177)[215,216], Gewald et al.[217] have recently shown that the product of reaction of (176a,b) with trichloroacetonitrile is really the pyridine derivatives (178) and (179) respectively. Convincing evidence from $^{13}C$ NMR in support with the proposed structures are reported (cf. Scheme 26)[217].



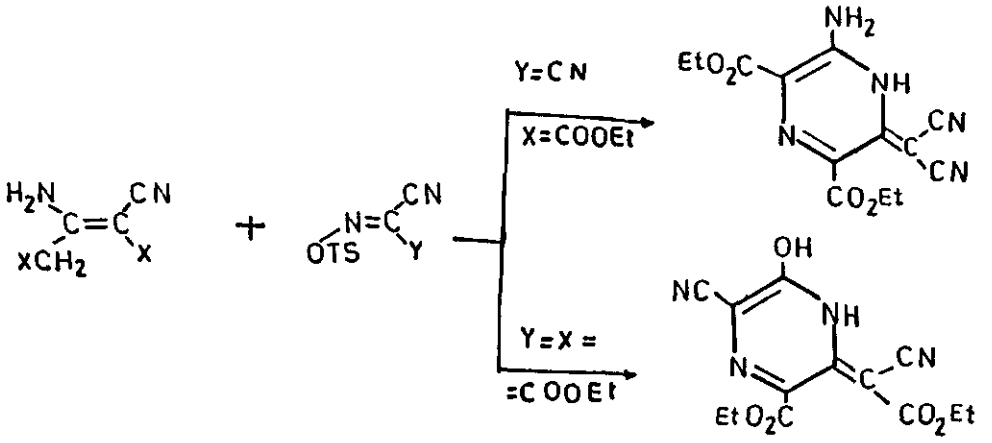

Another recently reported pyrimidine synthesis is summarized in the equation below (cf. Eq. 56)[218].



Eq.(56)

c. Synthesis of Pyrazines:

Only few examples for synthesis of pyrazines utilizing nitriles as starting materials have been reported. A demonstrated example for this synthetic approach is shown below (cf. Scheme 27)[219-221].

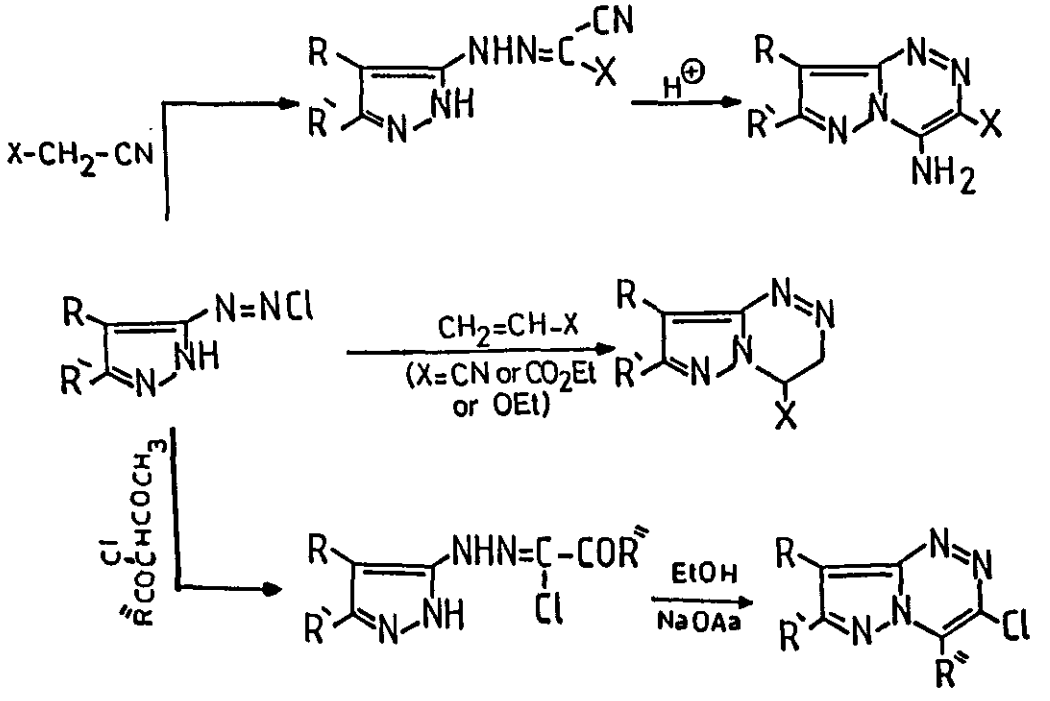



Scheme(27)

3. Synthesis of Six-Membered Rings with Three Hetero-Atoms:

a. Synthesis of Triazines:

In the following, the most interesting 1,2,4-triazine syntheses are summarized (cf. Scheme 28)[222-225].




Scheme(28)

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